

Soft Machines

Some personal views on nanotechnology, science and science policy from Richard Jones

Nanomedicine comes of age with mRNA vaccines

Richard Jones

November 13, 2020

Bio-nanotechnology

There have been few scientific announcements that have made as big an impact as the recent news that a vaccine, developed in a collaboration between German biotech company [BioNTech](#) and the pharmaceutical giant Pfizer, has been shown to be effective against covid-19. What's even more striking is that this vaccine is based on an entirely new technology. It's an mRNA vaccine; rather than injecting weakened or dead virus materials, it harnesses our own cells to make the antigens that prime our immune system to fight future infections, exactly where those antigens are needed. This is a brilliantly simple idea with many advantages over existing technologies that rely on virus material – but like most brilliant ideas, it takes lots of effort to make it actually work.

Here I want to discuss just one aspect of these new vaccines – how the mRNA molecule is delivered to the cells where we want it to go, and then caused to enter those cells, where it does its job of making the virus proteins that cause the chain of events leading to immunity. This relies on packaging the mRNA molecules inside nanoscale delivery devices. These packages protect the mRNA from the body's defense mechanisms, carry it undamaged into the interior of a target cell through the cell's protective membrane, and then open up to release the bare mRNA molecules to do their job. This isn't the first application of this kind of nanomedicine in the clinic – but if the vaccine lives up to expectations, it will make unquestionably the biggest impact. In this sense, it marks the coming of age of nanomedicine.

Other mRNA vaccines are in the pipeline too. One being developed by the US company [Moderna](#) with National Institute of Allergy and Infectious Diseases (part of the US Government's NIH), is also in phase 3 clinical trials, and it seems likely that we'll see an announcement about that soon too. Another, from the German Biotech company [CureVac](#), is one step behind, in phase 2 trials. All of these use the same basic idea, delivering mRNA which encodes a protein antigen. A couple of other potential mRNA vaccines use a twist on this simple idea; a candidate from [Arcturus](#) with the Duke-National University of Singapore, and another from [Imperial College](#), use "self-amplifying RNA" – RNA which doesn't just encode the desired antigen, but which also carries the instructions for some machinery to make more of itself. The advantage of this in principle is that it requires less RNA to produce the same amount of antigen.

But all of these candidates have overcome the same obstacle – how to get the RNA into the human cells where it is needed? The problem is that, even before the RNA reaches one of its target cells, the human body is very effective at identifying any stray bits of RNA it finds wandering around and destroying them. All of the RNA vaccine candidates use more or less the same solution, which is to wrap up the vulnerable RNA molecule in a nanoscale shell made of the same sort of lipid molecules that form the cell membrane.

The details of this technology are complex, though. I believe the BioNTech, CureVac and Imperial vaccines all use the same delivery technology, working in partnership with a Canadian biotech company [Acuitas Therapeutics](#). The Moderna vaccine delivery technology comes from that towering figure of nanomedicine, MIT's [Robert Langer](#). The details in each case are undoubtedly proprietary, but from the literature it seems that both approaches use the same ingredients.

The basic membrane components are a phospholipid analogous to that found in cell membranes (DSPC – distearoylphosphatidylcholine), together with cholesterol, which makes the bilayer more stable and less permeable. Added to that is a lipid to which is attached a short chain of the water-soluble polymer PEO. This provides the nanoparticle with a hairy coat, which probably helps the nanoparticle avoid some of the body's defences by repelling the approach of any macromolecules (artificial vesicles thus decorated are sometimes known as "stealth liposomes"), and perhaps also controls the shape and size of the nanoparticles. Finally, perhaps the crucial ingredient is another lipid, with a tertiary amine head group – an ionisable lipid. This is what the chemists call a weak base – like ammonia, it can accept a proton to become positively charged (a cation). Crucially, its charge state depends on the acidity or alkalinity of its environment.

To make the nanoparticles, these four components are dissolved in ethanol, while the RNA is dissolved in a mildly acidic solution in water. Then the two solutions are mixed together, and out of that mixture, by the marvel of self-assembly, the nanoparticles appear, with the RNA safely packaged up inside them. Of course, it's more complicated than that simple statement makes it seem, and I'm sure there's a huge amount of knowledge that goes into creating the right conditions to get the particles you need. But in essence, what I think is going on is something like this.

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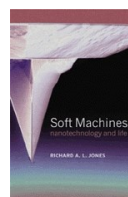


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When the ionisable lipid sees the acidic environment, it becomes positively charged – and, since the RNA molecule is negatively charged, the ionisable lipid and the RNA start to associate. Meanwhile, the other lipids will be self-organising into sheets two molecules thick, with the hydrophilic head groups on the outside and the oily tails in the middle. These sheets will roll up into little spheres, at the same time incorporating the ionisable lipids with their associated mRNA, to produce the final nanoparticles, with the RNA encapsulated inside them.

When the nanoparticles are injected into the patient's body, their hairy coating, from the PEO grafted lipids, will give them some protection against the body's defences. When they come into contact with the membrane of a cell, the ionisable lipid is once again crucial. Some of the natural lipids that make up the membrane coating the cell are negatively charged – so when they see the positively charged head-group of the ionisable lipids in the nanoparticles, they will bind to them. This has the effect of disrupting the membrane, creating a gap to allow the nanoparticle in.

This is a delicate business – cationic surfactants like CTAB use a similar mechanism to disrupt cell membranes, but they do that so effectively that they kill the cell – that's why we can make disinfectants out of them. The cationic lipid in the nanoparticle must have been chosen so that it disrupts the membrane enough to let the nanoparticle in, but not so much as to destroy it. Once inside the cell, the conditions must be different enough that the nanoparticle, which is only held together by relatively weak forces, breaks open to release its RNA payload.

It's taken a huge amount of work – over more than a decade – to devise and perfect a system that produces nanoparticles, that successfully envelopes the RNA payload, that can survive in the body long enough to reach a cell, that can deliver its payload through the cell membrane and then release it. What motivated this work wasn't the idea of making an RNA vaccine.

One of the earliest clinical applications of this kind of technology was for the drug Onpattro, produced by the US biotech company [Alnylam](#). This uses a different RNA based technology – so called small interfering RNA (siRNA) – to silence a malfunctioning gene in liver cells, to control the rare disease transthyretin amyloidosis. More recently, research has been driven by the field of cancer immunotherapy – this is the area for which the Founder/CEO of BioNTech, Uğur Şahin, received substantial funding from the European Research Council. Even for quite translational medical research, the path from concept to clinical application can take unexpected turns!

We all have to hope that the BioNTech/Pfizer vaccine lives up to its promise, and that at least some of the other vaccine candidates – both RNA based and more conventional – are similarly successful; it will undoubtedly be good to have a choice, as each vaccine will undoubtedly have relative strengths and weaknesses. The big question now must be how quickly production can be scaled up to the billions of doses needed to address a world pandemic.

One advantage of the mRNA vaccines is that the vaccine can be made in a chemical process, rather than having to culture viruses in a cell culture, making scale up faster. Of course there will be potential bottlenecks. These can be as simple as the vials needed to store the vaccine, or the facilities needed to transport and store them – especially acute for the BioNTech/Pfizer, which needs to be stored at -80° C.

There are also some quite specialised chemicals involved. I don't know what will be needed for scaling up RNA synthesis; for the lipids to make the nanoparticles, I believe that the Alabama-based firm [Avanti Polar Lipids](#) has the leading position. This company was recently bought, in what looks like a very well-timed acquisition, by the Yorkshire based speciality chemicals company [Croda](#), which I am sure has the capacity to scale up production effectively. Students of industrial history might appreciate that Croda was originally founded to refine Yorkshire wool grease into lanolin, so their involvement in this most modern application of nanotechnology, which nonetheless rests on fat-like molecules of biological origin, seems quite appropriate.

References.

The paper describing the BioNTech/Pfizer vaccine is: [Phase I/II study of COVID-19 RNA vaccine BNT162b1 in adults](#).

The key reference this paper gives for the mRNA delivery nanoparticles is: [Expression kinetics of nucleoside-modified mRNA delivered in lipid nanoparticles to mice by various routes](#).

The process of optimising the lipids for such delivery vehicles is described here: [Rational design of cationic lipids for siRNA delivery](#).

A paper from the Robert Langer group describes the (very similar) kind of delivery technology that I presume underlies the Moderna vaccine: [Optimization of Lipid Nanoparticle Formulations for mRNA Delivery in Vivo with Fractional Factorial and Definitive Screening Designs](#)

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Thanks for this very informative article. Been wondering how they were getting the RNA into cells.

Zelah

November 21, 2020 at 4:33 pm

Hi Richard,
Thankyou for your fascinating introduction to Nanomedicine. It has been a wild ride since the early 2000's. Finally nanoscience is reaching its promise!

I have a question. How will the UK's answer to Darpa prioritise Nanoscience? Is this even a good idea?
Thanks for everything.

Zelah

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